Can ErbB2 overexpression protect against doxorubicin cardiotoxicity?

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Identification of the human epidermal growth factor receptor (HER2/ErbB2) as a target for therapy in HER2/ErbB2-positive breast cancer was a huge milestone in treatment of these typically highly aggressive cancers. At 8-yr follow-up, trastuzumab, a monoclonal antibody against HER2/ErbB2, increased survival by ~40% compared with standard chemotherapy: anthracycline (doxorubicin), cyclophosphamide, and paclitaxel (11). Unfortunately, trastuzumab turned out to be severely cardiotoxic, leading to serious complications including left ventricular dysfunction and heart failure, with approximately three times greater incidence than anthracyclines (doxorubicin) alone (27 vs. 8% of patients at 1 yr of therapy) (14, 15). This is even further concerning when considering that anthracyclines themselves have considerable documented cardiotoxicity: ~8% at 1 yr, 6-18% at 2 yr (4, 13), and ~40% at 20 yr (5) postcompletion of treatment. As might be expected, because of the efficacy of anti-HER2/ErbB2 antibodies in the treatment of cancer, discovery of their cardiotoxicity prompted considerable research effort into mechanisms by which ErbB2 regulates cardiac function.

For over a decade, it has been known that a major increase in oxidative stress was the primary mechanism of doxorubicin-mediated cardiotoxicity (13). Oxidative stress has also been implicated as a mechanism for trastuzumab-induced cardiac dysfunction (6). ErbB2 antagonism in cardiac myocytes increased oxidative stress and cell death by increasing reactive oxygen species (ROS) and inducing mitochondrial apoptotic signaling (5). In this issue of the American Journal of Physiology-Heart and Circulatory Physiology, the study by Belmonte et al. (1) extends these findings to demonstrate that cardiac-specific ErbB2 overexpression is able to upregulate mitochondrial antioxidant defenses (glutathione peroxidase-1 expression, glutathione peroxidase activity, and catalase expression) and downregulate hydrogen peroxide in the mitochondria.

Mitochondrial oxidative stress plays a critical role in cardiovascular disease progression, including in the transition from compensatory hypertrophy to overt heart failure. Mitochondrial DNA (mtDNA) is more susceptible to damage by ROS due to lack of histones and thus greater accessibility to ROS and limited DNA repair enzyme capabilities in the mitochondria. Increased mtDNA damage translates into aberrant synthesis of proteins of the mitochondrial respiratory chain and eventual respiratory chain dysfunction (16). This then results in further ROS production, resulting in a cycle of amplification of ROS and mtDNA damage, which eventually leads to a critical drop in cellular ATP levels, Ca2+ overload, and myocyte death. Thus discovering that ErbB2 specifically modulates mitochondrial ROS levels in the heart may be important since this may elucidate the mechanism by which ErbB2 regulates mitochondrial and cardiac dysfunction.

In addition, the authors show that Abelson murine leukemia cellular oncogene homolog 1 (c-Abl) and Abelson-related gene (Arg) were upregulated by ErbB2 overexpression (1). c-Abl can transactivate the epidermal growth factor receptor through the Ras-Raf-extracellular signal recognition kinase 1/2 mitogen-activated protein kinase pathway as well as directly activate the phosphatidylinositol 3-kinase-Akt pathway (9), a major prosurvival signaling pathway in several cell types including cardiac myocytes. This is in agreement with the reported downregulation of Akt activation by ErbB2 antibodies in cancer cells and cardiac myocytes (5). Therefore, identification of these ErbB2-dependent signaling pathways in the heart in vivo are of potential translational significance with the goal of preserving cardiac function through decreasing myocyte cell death.

There are limitations in extending the novel mechanistic aspects of the present study to the function and therapeutic targeting of this system in vivo, which will need to be investigated in future studies. First, the effects of ErbB2 overexpression on cardiotoxicity are not examined in adult cardiac myocytes or in the whole heart in vivo. Cardiotoxicity is instead evaluated in neonatal myocytes in cell culture. Neonatal and adult myocytes differ in many significant parameters relevant to cell survival, including sensitivity to altered Ca2+ and ATP concentrations and oxygen consumption. Therefore, results from neonatal myocytes cannot be automatically translated to adult myocytes.

Second, while this study shows that ErbB2 overexpression in the heart increases certain aspects of the cellular antioxidant defense machinery and reduces ROS, it remains to be demonstrated if it is able to achieve this effect in the face of a doxorubicin or anti-HER2/ErbB2 antibody challenge, i.e., if the ErbB2 overexpressing animals were treated with a chemotherapeutically effective dose of doxorubicin and/or trastuzumab, would ErbB2 overexpression still be able to prevent the increase in ROS?

Third, this study demonstrates that ErbB2 overexpression maintains normal oxygen consumption and mitochondrial complex I activity. However, neither ATP production nor Ca2+ concentrations was measured. Increased mitochondrial ROS production is frequently coupled to decreased ATP production. Mitochondrial ATP production has been shown to be decreased specifically in doxorubicin-induced heart failure (2). Decreased ATP production leads to Ca2+ overload, mainly due to consequent failure of the sarcoplasmic reticulum Ca2+ ATPase 2 and the Na+/K+ ATPase leading to decreased activity of the Na+/Ca2+ exchanger, and heart failure. Therefore, it would be important to examine these parameters and cardiac function in future studies.

In summary, based on the findings presented in this study, it is difficult to form definitive conclusions regarding the protective effect of HER2/ErbB2 overexpression in the heart against doxorubicin- or trastuzumab-induced cardiotoxicity, either

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short or long term. Combined doxorubicine and trastuzumab regimen, constructed to mimic cycles of chemotherapy for HER2/ErbB2-positive breast cancer in humans, had a synergetic detrimental effect on both left and right ventricular function in mice, inducing biventricular failure in only 2 wk (7). Moreover, ventricular-restricted deletion of ErbB2 in mice resulted in multiple independent parameters of dilated cardiomyopathy, including chamber dilation, wall thinning, and decreased contractility (3). Thus evaluation of heart failure in ErbB2 overexpressing animals, or in the presence of an intervention that increases ErBb2 expression, in response to treatment with chemotherapeutically effective dose of doxorubicin and/or trastuzumab in future studies could help determine whether this system can protect against cardiac dysfunction caused by these agents.

A limitation of the majority of human and animal therapeutic studies related to doxorubicin and/or trastuzumab is that they do not consider an extended follow-up period. Similar to the study by Belmonte et al., a new pilot clinical trial with trastuzumab emtansine (TDM1), the HER2/ErbB2 antibody conjugated to a tubulin-binding agent that disrupts microtubule assembly, reported a 10% asymptomatic decline in left ventricular function in 3% of patients at a short 2-y follow-up and did not consider this significant (6). However, it is becoming increasingly apparent that doxorubicin-induced cardiotoxicity manifests as continual increase in incidence of sustained echocardiographic abnormalities, including overt heart failure, and affects ∼40% of patients 20 yr after conclusion of therapy (12) versus ∼8% at 1 yr posttherapy (14). Thus it might be advisable that future basic science animal studies and clinical studies that aim to evaluate cardiotoxicity of anthracycline- and HER2/ErbB2-based therapies extend follow-up time.

Overall, the study from Belmonte and colleagues (1), which examines the effects of cardiac-specific ErbB2 overexpression, provides novel evidence that it provides cardiac protection through upregulation of mitochondrial antioxidant defenses, glutathione peroxide 1 and catalase, and lowering of mitochondrial hydrogen peroxide. While this is likely to be an important target to prevents the pathological transition into overt heart failure, further studies are needed to establish its mechanism of action and potential therapeutic benefits. One potential mechanism is through preserving microvascular density. Coronary microvascular rarefaction has been associated with pathological (vs. exercise induced) cardiac hypertrophy and predicts transition to heart failure (dilated cardiomyopathy) (8). It has recently been demonstrated that decreasing specifically mitochondrial oxidative stress is necessary for restoration of coronary arteriogenesis (11). Similar, mitocondrial oxidative, stress-dependent mechanisms could also apply to angiogenesis. Erb2B overexpression, because it apparently regulates mitochondrial oxidative stress, could feasibly facilitate both processes.

GRANTS
This work is supported by National Heart, Lung, and Blood Institute Grant R01-HL093052.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS
P.R. drafted, edited and revised, and approved final version of manuscript.

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